# Drug-Drug, Drug–Dietary Supplement, and Drug–Citrus Fruit and Other Food Interactions: What Have We Learned?

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*Serious drug-drug interactions have contributed to recent U.S. market withdrawals and also recent nonapprovals of a few new molecular entities. Many of these interactions involved the inhibition or induction of metabolizing enzymes and efflux transporters, resulting in altered systemic exposure and adverse drug reactions or loss of efficacy. In addition to drug-drug interactions, drug–dietary supplement and drug–citrus fruit interactions, among others, could also cause adverse drug reactions or loss of efficacy and are important issues to consider in the evaluation of new drug candidates. This commentary reviews (1) the current understanding of the mechanistic basis of these interactions, (2) issues to consider in the interpretation of study results, and (3) recent labeling examples to illustrate the translation of study results to information useful for patients and health care providers.*

***Keywords:*** *Drug-drug interaction; drug–dietary supplement interaction; drug-juice interaction; drug development; exposure-response relationship; labeling; risk management*

***Journal of Clinical Pharmacology, 2004;44:559-569***


Serious drug-drug interactions have contributed to half of the recent U.S. market withdrawals of approved drugs and also to recent nonapprovals of a few new molecular entities (see Table I). Many of these interactions involved inhibition of metabolizing enzymes and efflux transporters, resulting in increased systemic exposure and subsequent adverse drug reactions. In other cases, induction of cytochrome P450 enzymes and/or transferases and transporters resulted in reduced systemic exposure and a risk of loss of efficacy of coadministered drugs. In addition to drug-drug interactions, drug–dietary supplement and drug–citrus fruit interactions, among others, are emerging as important issues to consider in the evaluation of new drug candidates. A recent survey[1] indicated that in the United States, multiple drug use is common. More than 50% of individuals in a given week would be taking at least 1 prescription drug, and more than 7% would be taking at least 5 prescription drugs.[1] When all medications (including prescription drugs, over-the-counter drugs, vitamins/minerals, and herbal supplements) are considered, more than 81% of individuals would be taking at least 1 medication in a given week, and more than 25% would be taking at least 5 medications.[1] The same survey indicated that the highest overall prevalence of medication use was among women at least age 65 years, of whom 12% took at least 10 medications and 23% took at least 5 prescription drugs.[1]

The increasing use of dietary supplements presents a special challenge in managing patients' health care. In AIDS and cancer patients, the use of multiple prescription drugs and dietary supplements is, in particular, prevalent.[2,3] Depending on the level of evidence for the above interactions, the Center for Drug Evaluation and Research (CDER) may make the decision to incorporate information about these interactions in drug labeling as one of the initial steps toward risk communications to health providers and patients.

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DOI: 10.1177/0091270004265367

**Table I** Examples of Drugs Withdrawn from the U.S. Market or Not Approved between 1998 and 2003

| Year | | | | |
|---|---|---|---|---|
| Withdrawn | Approval | Drug Name[a] | Use | Risk |
| 1998 | 1997 | Mibefradil (Posicor) | High blood pressure/ chronic stable angina | Drug-drug interactions, torsades de pointes |
| 1998 | 1997 | Bromfenac (Duract) | NSAID | Acute liver failure |
| 1998 | 1985 | Terfenadine (Seldane/Seldane-D) | Antihistamine | Torsades de pointes, drug-drug interactions |
| 1999 | 1988 | Astemizole (Hismanal) | Antihistamine | Torsades de pointes, drug-drug interactions |
| 1999 | 1997 | Grepafloxacin (Raxar) | Antibiotics | Torsades de pointes |
| 1999 (NA) | | Drug A | | Torsades de pointes, drug-drug interactions |
| 2000 | 2000 | Alosetron[b] (Lotronex) | Irritable bowel syndrome in women | Ischemic colitis, complications of constipation |
| 2000 | 1993 | Cisapride (Propulsid) | Heartburn | Torsades de pointes, drug-drug interactions |
| 2000 | 1997 | Troglitazone (Rezulin) | Diabetes | Acute liver failure |
| 2001 | 1997 | Cerivastatin (Baycol) | Cholesterol lowering | Rhabdomyolysis, drug-drug interactions |
| 2001 | 1999 | Rapacuronium bromide (Raplon) | Anesthesia | Bronchospasm |
| 2001 (NA) | | Drug B | | Drug-drug interactions |

NA, not approved.
a. Trade names are in parentheses.
b. Reintroduced to the market in 2002 with use restricted to patients severely affected with irritable bowel syndrome.

## DRUG-DRUG INTERACTIONS

Recognizing the importance of evaluating the drug interaction potential early in drug development, pharmaceutical companies have routinely assessed a new molecular entity's clearance pathways and its enzyme/transporter-modulating effects during early drug development.[4-7] As cytochrome P450 (CYP) enzymes have been involved in many clinically important drug interactions, in vitro evaluation of a drug's metabolic pathways and its modulation effects on CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A activities has been a critical first step in this evaluation. Depending on the outcome of this in vitro evaluation using human liver tissues or expressed human enzymes, subsequent clinical studies may be conducted to answer specific questions about drug interaction. In addition to CYP enzymes, various other metabolic enzymes (e.g., glucuronosyl transferases) and transporters (e.g., P-glycoprotein [P-gp], organic anion transporting peptide [OATP], and multidrug resistance protein [MRP]) also play important roles in drug interactions and changes in systemic exposure.[8-12] The use of complementary approaches (e.g., population pharmacokinetic assessments) can provide additional opportunities to uncover unexpected pharmacokinetic drug interactions and, with proper design, pharmacodynamic interactions.

In addition to published reports, documents have been developed and are available to provide guidance to industry and agency reviewers regarding the use of various methodologies to investigate drug-drug interactions.[13,14] As the science progresses, revision of these documents is necessary to address labeling and other emerging issues.[15-17] Recent public workshops and industry working groups have also produced useful information about the evaluation of drug interactions.[18,19]

The clinical significance of increases or decreases in the systemic exposure of coadministered drugs found in clinical studies conducted in healthy subjects or patient populations should be determined based on the known relationships between dose and/or plasma concentrations and biomarkers of efficacy or safety.[20] When evaluating the significance of a pharmacokinetic interaction, it is usually assumed that the pharmacokinetic-pharmacodynamic (PK-PD) relationship of a drug is unchanged in the presence of other drugs. Recommendations based on this relationship can then be made with respect to changing the dose, adjusting the dosing interval, or including suitable language in the labeling, "precautions/warnings," or "contraindications." Figure 1a illustrates that, via evaluation of the relationship between exposure (dose, AUC, $C_{max}$, etc.) and response (key efficacy and safety measures, either clinical endpoints, surrogate endpoints, or valid biomarkers), a range of systemic expo-

**Table II** Examples of Recent Labeling on Drug-Drug Interactions (Rosuvastatin)[23]

| Coadministered Drug | Rosuvastatin AUC Fold-Change (Mean) | Rosuvastatin $C_{max}$ Fold-Change (Mean) | Rosuvastatin Labeling |
|---|---|---|---|
| | | | Approved dosing: 5-40 mg once daily; usual recommended starting dose: 10 mg once daily |
| Cyclosporine | 7 | 11 | "Patients taking cyclosporine . . . limited to 5 mg once daily" |
| Gemfibrozil | 2 | 2 | "Combination with gemfibrozil . . . limited to 10 mg once daily" |

**Table III** Examples of Recent Labeling on Drug-Drug Interactions (Vardenafil)[24]

| Coadministered Drug | Vardenafil AUC Fold-Change (Mean) | Vardenafil $C_{max}$ Fold-Change (Mean) | Vardenafil Labeling |
|---|---|---|---|
| | | | Approved dosing: 5-20 mg daily; recommended starting dose: 10 mg once per day |
| Ritonavir (600 bid) | 49 | 13 | "< 2.5 mg . . . not exceeded in 72 hr . . . taking ritonavir" |
| Indinavir (800 tid) | 16 | 7 | "< 2.5 mg daily . . . taking indinavir, ketoconazole 400 mg daily, itraconazole 400 mg daily" |
| Ketoconazole (200 qd) | 10 | 4 | "< 5 mg daily . . . taking ketoconazole/itraconazole 200 mg daily, or erythromycin" |
| Erythromycin (500 tid) | 4 | 3 | |

sures corresponding to effective and safe administration can be determined. With this information, rational dose adjustments can be made to achieve target systemic exposure when interacting drugs are coadministered. In some cases, it may not be necessary to adjust the dose or dosing regimen as the changes in exposure would still be within the therapeutic range of exposure defined in other clinical trials. Therefore, doses (usually lower) or dosing regimens not tested clinically can be recommended if these adjusted doses or dosage regimens in patients in certain conditions (e.g., presence of an enzyme inhibitor or hepatic dysfunction) would provide similar systemic exposure as that in patients without these conditions. For example, rosuvastatin, a HMG CoA reductase inhibitor, was recently approved for the treatment of hypercholesterolemia and mixed hyperlipidemia. Data from various Phase II clinical trials showed dose-related increases in the extent of low-density lipoprotein (LDL) lowering in patients given 1 to 80 mg for 6 weeks.[21] There were also dose- or concentration-related increases in the occurrence rates of rhabdomyolysis, myopathy, or proteinuria.[22] Based on the efficacy and safety data contained in the new drug application, doses of 5 to 40 mg once daily were approved[23] (with a usual recommended starting dose of 10 mg once daily). Figure 1b illustrates the relationship between the approved doses and their efficacy and safety. Table II shows results of some interaction studies and the recommended doses (5-10 mg) of rosuvastatin when patients are to take certain other drugs.[23] Table III shows results of key interaction studies and the recommended doses when vardenafil, recently approved for erectile dysfunction, is administered with various cytochrome P450 inhibitors. Note that the approved doses are 5 to 20 mg once per day (with a recommended starting dose of 10 mg). Figure 1c illustrates the relationship between the dose and efficacy and safety. The recommended doses and dosing regimens range from 2.5 mg every 3 days to 5 mg per day[24] when vardenafil is administered with cytochrome P450 inhibitors to achieve systemic exposure levels within those known to correspond to safe and effective use of the drug.

## DRUG–DIETARY SUPPLEMENT INTERACTIONS

### St. John's Wort

St. John's wort, a dietary supplement often used for depression,[25] is one of the top-selling dietary supplements in the United States. Although current products are standardized based on hypericin levels, hyperforin

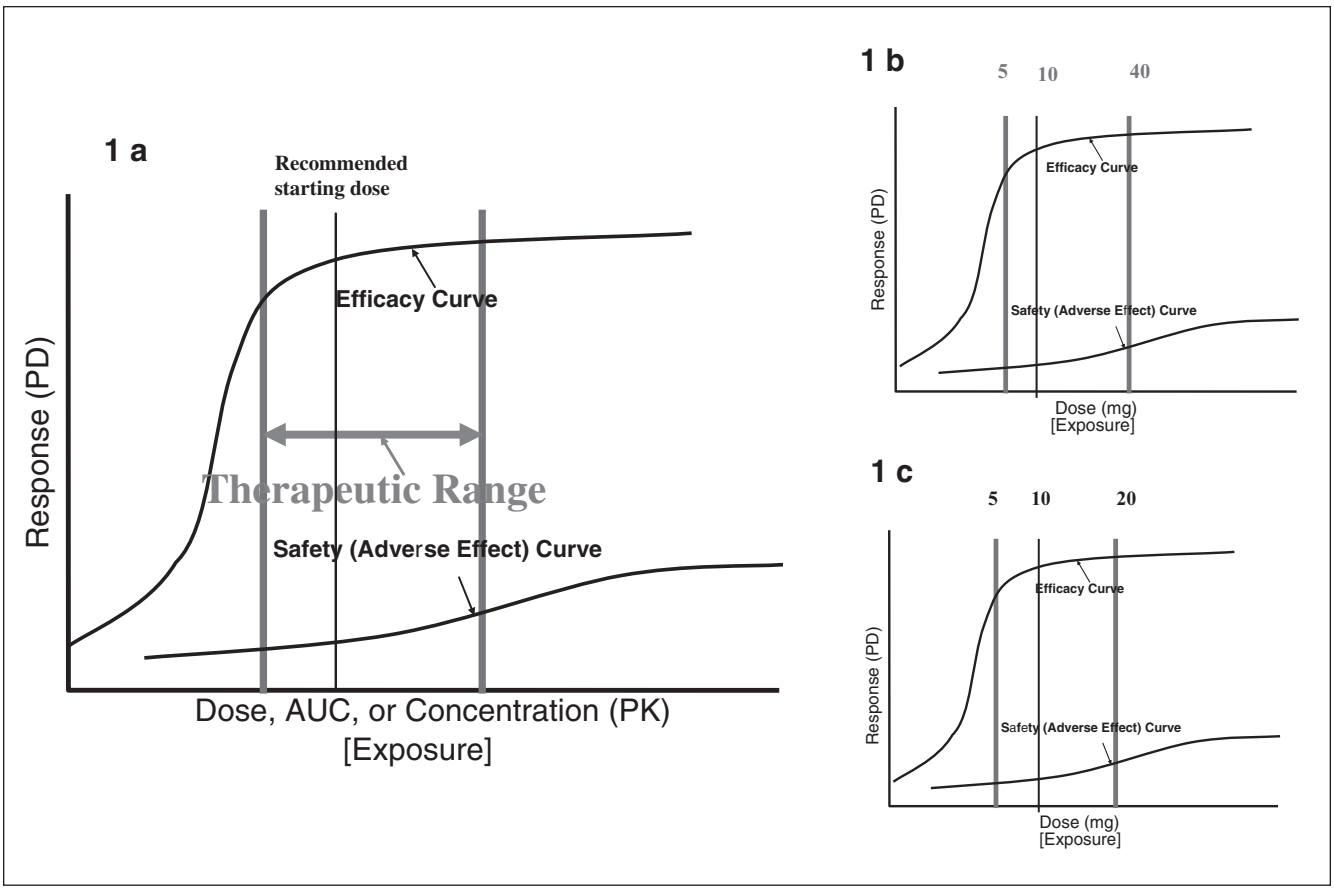


*Figure 1. Hypothetical exposure-response relationship. a) Determination of a therapeutic range based on exposure (dose, AUC, $C_{max}$, etc.) and response data.[4] (b) An example of when the safe and effective doses range from 5 to 40 mg (recommended starting dose: 10 mg). (c) An example of when the safe and effective doses range from 5 to 20 mg (recommended starting dose: 10 mg).*

appears to be one of the main components, with selective serotonin reuptake inhibitor (SSRI) activity in vitro. Hyperforin also appears to be the more potent inducer of CYP3A enzymes based on in vitro studies.[26]

Following reports of reduced plasma levels of indinavir in healthy subjects when St. John's wort was coadministered,[27] as well as reports of heart transplant rejection with corresponding decreases in plasma levels of cyclosporine in patients taking St. John's wort while on cyclosporine,[28] the Food and Drug Administration (FDA) issued a health advisory in February 2000 stating that "concomitant use with protease inhibitors or non-nucleoside reverse transcriptase inhibitors is not recommended."[29] A search of FDA adverse events reporting databases in both the CDER and the CFSAN (Center for Food Safety and Applied Nutrition) on St. John's wort up to July 2002 resulted in 498 reports, including 42 that implicated St. John's wort's possible role in the varied responses of cyclosporine (rejection, lowered plasma levels), oral contraceptives (breakthrough bleedings, pregnancy), sildenafil (loss of efficacy), and so on.[30]

Subsequently, the CDER and the FDA Office of Women's Health sponsored prospective clinical studies to understand the underlying mechanisms of interactions between St. John's wort and these drugs. Using a cocktail approach, midazolam (via oral and intravenous administration), caffeine, dextromethorphan, and tolbutamide were administered to healthy human subjects to evaluate activities of CYP3A (intestinal and hepatic), CYP1A2, CYP2D6, and CYP2C9, respectively. St. John's wort appeared to have minimal effects on these enzymes after acute administration (900 mg). In contrast, chronic administration (2 weeks) of St. John's wort (300 mg three times a day) selectively induced CYP3A, with a greater effect in the small intestine than in the liver.[31] In a similarly designed study using fexofenadine as a probe drug for the P-gp transporter,

acute dosing of St. John's wort slightly increased fexofenadine levels.[32] These increases were, however, reduced to baseline after 2 weeks of daily dosing of St. John's wort. Another study evaluating St. John's wort's effects on the clearance of a low-dose oral contraceptive showed that 8 weeks of St. John's wort treatment decreased plasma levels of norethindrone and reduced the $t_{1/2}$ of ethinyl estradiol,[33] consistent with increased CYP3A activity. In this study, more breakthrough bleeding was found in the St. John's wort treatment phase as compared to the control phase (7/12 vs. 2/12). Incidentally, the midazolam clearance measured in this study showed a twofold higher clearance in the subjects with breakthrough bleeding as compared to those without.[33]

### *Impact on Drug Labeling*

Based on the mechanistic information, the current labeling recommendation is that for drugs that are substrates of CYP3A or P-gp and in which the products' effectiveness may be reduced upon coadministration of St. John's wort, St. John's wort may be listed along with other known inducers, such as rifampin and rifabutin, in the labeling as possibly decreasing plasma levels. For example, Kaletra (lopinavir and ritonavir), Mifeprex (mifepristone, RU486), Nuvaring (etonogestrel/ethinyl estradiol), Gleevec (imatinib), Neoral (cyclosporine), Rapamune (sirolimus), and Prograf (tacrolimus) have information about St. John's wort in various sections of their labeling.[34] In addition, several St. John's wort products carry labeling information such as the following: "St. John's Wort can have potentially dangerous interactions with some prescription drugs. Consult your physician before taking St. John's Wort if you are currently taking anticoagulants, oral contraceptives, antidepressants, anti-seizure medications, drugs to treat HIV or prevent transplant rejections, or any other prescription drug."[35]

### Echinacea

Echinacea, often used for the treatment of cold and viral infection, is another one of the top-five selling products in the United States. In vitro liver microsomal studies showed that echinacea may affect the activity of metabolizing enzymes.[36] The effect of echinacea on CYP3A, CYP1A2, CYP2D6, and CYP2C9 in healthy human subjects was studied using a cocktail approach as described previously for St. John's wort. After 8 days of administration of 400 mg four times a day of an echinacea product, CYP2C9 and CYP2D6 activities were not changed significantly. On the other hand, CYP1A2 and intestinal CYP3A activities were inhibited while hepatic CYP3A was induced.[37] Based on these preliminary findings, the effect of echinacea on various CYP3A substrates may vary depending on the relative contribution of intestinal CYP3A versus the hepatic CYP3A in the individual substrate's clearance pathway to a given drug's overall clearance.

### Ginkgo Biloba

Ginkgo biloba, often used for memory improvement, is another one of top-five selling products in the United States. In vitro liver microsomal studies showed that ginkgo products affect the activity of metabolizing enzymes.[38] The clinical effect of ginkgo on various metabolizing enzymes has been evaluated with a cocktail approach.[38] This ginkgo product (ginkgo biloba extract EGb761) was shown to induce CYP2C19 based on the changes in plasma AUC ratios of a probe drug and its metabolite, omeprazole/5-hydroxyomeprazole. The extent of induction appeared to be CYP2C19 genotype dependent.[39]

### *Impact on Clinical Study Design*

To avoid variable outcomes due to the uncontrolled use of dietary supplements during clinical trials, it is important to include their use in the exclusion criteria. An example of statements in a study protocol includes the following: "Participants will be excluded for the following reasons: . . . use of prescription or over-the-counter medications, *including herbal products*, or alcohol within two weeks prior to enrollment."

## DRUG–CITRUS FRUIT AND OTHER FOOD INTERACTIONS

### Grapefruit Juice Effects on CYP3A

Literature data suggest that grapefruit juice inhibits intestinal CYP3A and other enzymes. Figure 2 shows percent changes in AUC values when grapefruit juice was ingested (vs. without grapefruit juice) with various drugs from a sample of studies.[12,40-50] The percent change ranged from 0% (pravastatin), 60% (cyclosporine), 230% (atorvastatin), to 1250% to 1400% (lovastatin/simvastatin). This wide range of increases in AUC reflects the varying percent contribution of CYP3A to the overall clearance process of individual substrates mentioned above. In addition, the extent of interactions varies widely among subjects in a given study and between studies, possibly due to (1) the interindividual variability of baseline intestinal

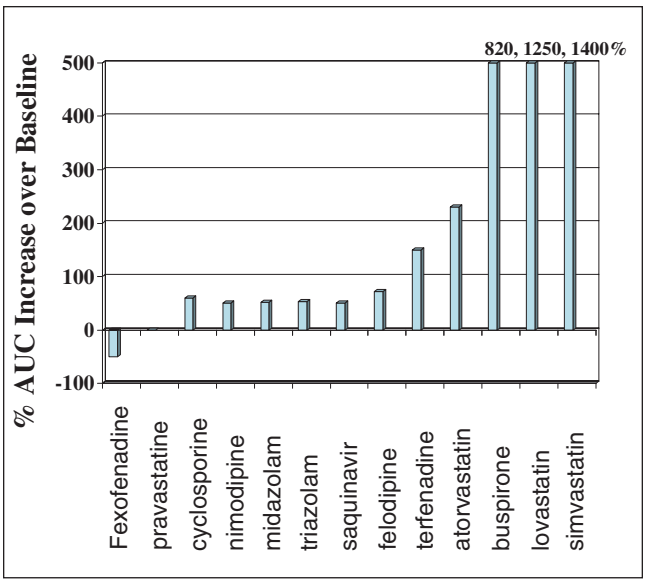


*Figure 2. Examples of AUC changes over baseline when the drug was given with grapefruit juice.*[12,40-50]

CYP3A levels[51,52] and (2) the differences in study design, including the timing of grapefruit juice administration relative to drug administration, the various brands and preparations of grapefruit juice used, the amount of grapefruit juice consumed, and so on.

A search of FDA adverse events ending in January 2002 resulted in 36 cases implicating grapefruit juice in possible interactions. These included cases with observed extension of pharmacological effects for calcium channel blockers (resulting in hypotension), statins (leading to muscle pain), antihistamines (resultant cardiac effects), and others.[53] One report indicated that a 69-year-old male on lovastatin (and gemfibrozil, among other medications) developed diffuse muscle pain and a high creatine phosphate kinase level (400-fold higher than normal) within 2 weeks after switching from his usual orange juice to grapefruit juice. The reporting physician suggested interactions between grapefruit juice and lovastatin and gemfibrozil and recommended that the patient avoid grapefruit juice.[53-55]

### *Impact on Drug Labeling*

The current labeling recommendation is that for drugs that are primarily substrates of CYP3A with low oral bioavailability, grapefruit juice may be listed along with other CYP3A inhibitors, such as ketoconazole and erythromycin, in the labeling as possibly increasing plasma levels of coadministered drugs. For example, cyclosporine, sirolimus, simvastatin, and lovastatin have information on a grapefruit juice interaction in various sections of their labeling.[34]

### Grapefruit Juice, Apple Juice, and Orange Juice Effects on Transporters

Grapefruit juice appears to also inhibit P-gp,[56] and this may be one of the mechanisms for the increase in cyclosporine levels when cyclosporine is given with grapefruit juice. Fexofenadine is a P-gp substrate.[57] However, instead of increasing plasma levels of fexofenadine, consumption of a large quantity (1200 mL or 40 oz) of grapefruit juice, apple juice, or orange juice, respectively, decreased plasma levels of fexofenadine.[12] In vitro evaluations showed that fexofenadine is also a substrate of an uptake transporter in the intestine (OATP) and that fruit juices studied are more potent inhibitors of OATP than P-gp. This may explain the observed decreased fexofenadine plasma levels (Figure 2).

### Calcium-Fortified Orange Juice Effect on Bioavailability

Several studies have shown a modest effect of calcium-fortified orange juice on the absorption of fluoroquinolones. For example, studies on levofloxacin, gatifloxacin, and ciprofloxacin showed that $C_{max}$ was decreased by 11%, 15%, and 41%, respectively, when these drugs were given with calcium-fortified orange juice.[58-60] Chemical complexation of the floxacins with the calcium ion may play a major role in the reduced absorption and decreased plasma levels. The current labeling for Cipro (ciprofloxacin) tablets has the following information for patients: "As with other quinolones, concurrent administration of ciprofloxacin with magnesium/aluminum antacids, or sucralfate, Videx® (didanosine) . . . or with other products containing calcium, iron or zinc should be avoided. Ciprofloxacin may be taken two hours before or six hours after taking these products. Ciprofloxacin should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone since absorption of ciprofloxacin may be significantly reduced; however, ciprofloxacin may be taken with a meal that contains these products."[34]

### Cranberry Juice

Cranberry juice has been used to reduce the recurrence of urinary tract infection.[61] Recently, the British Com-

mittee on Safety of Medicines reported five cases of excessive warfarin anticoagulation and implicated cranberry juice as the interacting component. In its report of "current problems in pharmacovigilance,"[62] it described one fatal case[63] in which a patient's international normalized ratio (INR) was greater than 50 six weeks after starting cranberry juice and warned that "patients taking warfarin should limit or avoid drinking cranberry juice." Although cranberry juice contains antioxidants (flavonoids) that may affect cytochrome P450 enzymes, other factors may have contributed to this case.[64] Additional studies will be needed to determine the clinical significance of possible interactions of cranberry juice with drugs that are substrates of various cytochrome P450 enzymes and transporters.

### *Impact on Clinical Study Design*

To avoid variable outcomes due to the uncontrolled use of juices or other foods that may affect various metabolizing enzymes and transporters during clinical trials, it is important to consider their exclusion during the study period. Depending on the clearance pathway of the drug being evaluated, statements in a study protocol may include the following: "For at least 2 weeks prior to the start of the study until its conclusion, volunteers will not be allowed to eat any food or drink any beverage containing *alcohol, grapefruit or grapefruit juice, apple or orange juice, vegetables from the mustard green family* (e.g., kale, broccoli, watercress, collard greens, kohlrabi, brussels sprouts, mustard), and *charbroiled meats*."

## INTERACTION STUDIES IN SPECIFIC POPULATIONS

### Gender

Earlier clinical interaction studies enrolled mostly healthy male subjects. An earlier survey of new drug applications submitted to the CDER between 1994 and 1995 showed that females constituted only one-third of subjects in drug interaction studies.[4] There have only been limited publications with by-gender analysis of drug interaction data. In an evaluation of the inhibition effect of clarithromycin on midazolam, a sensitive CYP3A substrate, Gorski et al[65] showed greater effects on exposure in female subjects as compared to male subjects, that is, an 11-fold versus 5-fold increase in midazolam AUC after oral dosing. In contrast, when tirilazad, a CYP3A substrate, was coadministered with phenobarbital, an inducer of CYP3A, there was no apparent gender differences in the extent of interactions.[66]

### Pharmacogenetics

Many metabolizing enzymes are polymorphically distributed. This may account for the large intersubject variability observed in plasma levels and responses of certain drugs that are substrates of these enzymes. For example, genetic variability in the activity of cytochrome P450 enzymes (e.g., CYP2D6, CYP2C9, CYP2C19, and CYP3A5), Phase II metabolizing enzymes (e.g., UGT1A1 and TPMT), and transporters (e.g., ABCA1, ABCB1, and ABCC) has been reported. Subjects with different genotypes may show a different extent of interactions. For example, a study evaluating the effect of diphenhydramine, a modest CYP2D6 inhibitor, on metoprolol pharmacokinetics showed an increase (60%) in the plasma AUC of metoprolol in CYP2D6 extensive metabolizers (EMs). In contrast, little or no significant changes (10%) in AUC were observed in poor metabolizers (PMs).[67] More recently, the labeling of atomoxetine (Strattera), a CYP2D6 substrate, states, "For PMs, AUC of atomoxetine is approximately 10-fold and $C_{ss,max}$ is about 5-fold greater than EMs" and "coadministration of cytochrome P450 inhibitors to PMs (poor metabolizers) will not increase the plasma concentrations of atomoxetine."[34] In another example, Chow et al[38,39] showed that when ginkgo biloba was given with a cocktail of probe drugs for various cytochrome P450 enzymes, ginkgo induced omeprazole clearance to different degrees in different genotypes of CYP2C19. The genotype of the major metabolizing enzyme can influence the extent of interaction of the drug with inhibitors of minor pathways. For example, Brynne et al[68] showed that in CYP2D6 poor metabolizers, the clearance of tolterodine, which is mainly metabolized by CYP2D6 with a small contribution by CYP3A, was significantly reduced by a CYP3A inhibitor, ketoconazole.

## CONCLUSIONS

Drug-drug interactions contributed significantly to adverse drug reactions.[69] As part of preapproval risk assessment, the CDER has issued various guidance documents addressing study design, data analysis issues in the evaluation of drug interactions of new molecular entities (NMEs), and recommendations on drug labeling.[13,14] An understanding of the clearance pathways of an NME and its modulating effects of CYP enzymes and certain transporters is essential in predicting human drug interactions and understanding possible mechanisms of these interactions. Once an interaction is projected and observed, its clinical significance will de-

**Table IV** Examples of Management of Drug-Drug, Drug–St. John's Wort, and Drug–Grapefruit Juice Interactions of Various Drugs[34,76]

| Drug Name | Labeling Section | Labeling |
|---|---|---|
| Eletriptan (Relpax) labeling, December 2002[34] | WARNINGS | "Eletriptan should not be used within at least 72 hours of treatment with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir. Eletriptan should not be used within 72 hours with drugs that have demonstrated potent CYP3A4 inhibition and have this potent effect described in the CONTRAINDICATIONS, WARNINGS or PRECAUTIONS sections of their labeling (see CLINICAL PHARMACOLOGY: Drug Interactions and DOSAGE AND ADMINISTRATION)." |
| Mibefradil (Posicor), June 12, 1998 | —[a] | "It takes an average of 7 days, but can take up to 14 days, for sufficient elimination of the metabolites of Posicor to minimize the inhibition of CYP 450 system." |
| Cyclosporine (Neoral) labeling, January 2001 | PRECAUTIONS | "Patients should be advised to take Neoral® on a consistent schedule with regard to time of day and relation to meals. Grapefruit and grapefruit juice affect metabolism, increasing blood concentration of cyclosporine, thus should be avoided." |
| Ritonavir and lopinavir (Kaletra) labeling, January 2002 | WARNINGS: Drug Interactions | "Concomitant use of KALETRA and St. John's wort (hypericum perforatum), or products containing St. John's wort, is not recommended." |

a. "Dear Doctor" letter issued after mibefradil was withdrawn from the U.S. Market.[76]

pend on a known exposure-response relationship for the efficacy and safety of the particular drugs that are affected.[14,20]

With the increased understanding of the mechanisms of drug interactions of certain dietary supplements (e.g., St. John's wort) and juices (e.g., grapefruit juice), one can project the likelihood of an interaction with a drug depending on the drug's clearance pathway. However, unlike drug products in which the content and interacting components are better understood, information on the active components (responsible for drug interactions) and the contents of dietary supplements and juices is limited. Therefore, current labeling recommendations to avoid drug–dietary supplements and drug–fruit juice interactions are more restrictive than those for drug-drug interactions. As shown in Tables II to IV, certain drug-drug interactions can be managed by adjusting the dose or dosing interval of interacting drugs. However, drug–dietary supplement or drug-juice interactions may only be managed by recommending avoidance of their concomitant use when the interactions are deemed clinically significant. With increased understanding of interacting mechanisms[12,26,31,32,36-39,51,52,70] and the characterization of the various active components in dietary supplements and juices, as well as their pharmacokinetics,[71] more specific guidance to address these interactions in the future may be possible.

Despite the increased understanding and documentation of drug interactions in the labeling and in letters to "dear health care professionals," well-understood drug interactions continue to be reported.[72-74] To address this critical issue of translating information to practice, the CDER has published a proposed rule on a physician's labeling format whereby drug interactions that are significant—or their absence, when they are expected to occur—would appear in the Highlights section, in addition to having this information in the main body of the labeling.[17] Additional measures to address patient risks from drugs (e.g., medication guides, restricted distribution, prescriber certification) have been recommended in recently issued draft documents on risk management.[75]

In conclusion, with continued improvement in our understanding of the mechanisms of interactions and contributions of additional patient factors (e.g., genetics, gender), the risks associated with these interactions can be better predicted, assessed, and managed to reduce the frequency of clinically significant adverse drug reactions.

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